

REMARKS

Currently, claims 1-14 and 22-65 are pending in the present application. Applicant wished to express his gratitude to the Examiner for withdrawing the previous objection to claim 4-21 and 25-28. Additionally, Applicant is grateful to the Examiner for withdrawing rejection of claims 1-28 and 57-59 that was made under 35 USC 112 (second paragraph). Applicant has added new claims 66-68. No new matter has been entered as a results of these amendments.

Rejection of claims 1-14, 22-28, 57-59 and 63-65 under 35 USC § 103(a)

Claims 1-14, 22-28, 57-59 and 63-65 are rejected under 35 USC 103(a) as being unpatentable over Davison *et al.* (4,879,303) and Borge *et al.* (5,385,929) in view of Jukema (Arteriosclerosis, Thrombosis, and Vascular Biology, v16, No. 3 (1996), pp425-430) and Merck Index. Applicant respectfully disagrees.

The Examiner states that Davison teaches "a pharmaceutical composition comprising amlodipine besylate useful in treating ischemic heart disease ..., see claim 1 and abstract in particular." The Examiner continues, "Bjorge ... teaches a pharmaceutical composition comprising ... metabolites of atorvastatin and a pharmaceutical carrier useful in inhibiting cholesterol synthesis ... see claims 12, 18 and abstract."

The Examiner adroitly points out that "Davison ... and Bjorge ... taken together do not expressly disclose a [pharmaceutical] composition comprising amlodipine besylate and a hydroxylated metabolite of atorvastatin." Applicant completely concurs with this assessment made by the Examiner.

The Examiner, however, states that "[Jukema] ... discloses the evidence for a synergistic effect of calcium channel blockers ... with lipid-lowering therapy in retarding progression [of] coronary atherosclerosis ..." The examiner continues, "[t]he lipid-lowering agents employed therein in the combined therapy are HMG-CoA reductase

inhibitors such as pravastatin ..." Continuing, "[o]ne of calcium channel blockers employed therein is amlodipine ..."

The Examiner next addresses the Merck Index stating that the Index "lists atorvastatin as a HMG-CoA Reductase Inhibitor, belonging to the same therapeutic group as Pravastatin ..."

The Examiner concludes by stating, "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to employ amlodipine besylate with atorvastatin metabolites in a [pharmaceutical] composition."

In order to establish a *prima facie* case of obviousness, "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references) must teach or suggest all of the claim limitations." M.P.E.P. §2143, see also, *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Moreover, it is axiomatic in patent law that if an independent claim defines allowable subject matter then the claims depending therefrom also define allowable subject matter. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), and *Hartness International, Inc. v. Simplimatic Engineering Co.*, 819 F.2d 1100, 1108, 2 USPQ2d 1826, 1831 (Fed. Cir. 1987). Given that the rejected claims depend from base claims and those independent claims define allowable subject matter, then the claims at issue must necessarily define allowable subject matter. The reasons for allowability of the base claims are set forth herein.

Neither Davison nor Bjorge, alone or in combination with either Jukema and/or the Merck Index, provides a sufficient case of *prima facie* obviousness. The cited references neither teach nor suggest the presently claimed invention. For example, these

cited references alone or in combination do not teach or suggest a combination therapy using amlodipine and an atorvastatin metabolite for synergistically inhibiting lipid peroxidation in LDL or membrane lipid bilayers, and/or for use as an antioxidant.

The Examiner states that neither Davison nor Bjorge alone teach or suggest the present invention. However, the Examiner employs Jukema *et al.* as a reference that allegedly supplies that which is deficient in Davison and Bjorge. The Examiner contends that Jukema *et al.* disclose evidence for a synergistic effect of calcium channel blockers with lipid-lowering therapy.

In fact, Jukema does not provide evidence for a synergistic effect. Attached hereto is a signed declaration from Dr. Jukema (see, Exhibit A). In his declaration, referring to his own paper which is cited by the Examiner, he states that "we did not conduct any original experiments for this analysis of the REGRESS study, such as data showing a *synergistic effect* using a combination therapy comprising amlodipine and atorvastatin (or any of their analogs)." [*italics added*] See paragraph 4 of Jukema Declaration. Therefore, an inference cannot be drawn from Jukema's work that a combination of amlodipine and atorvastatin has any synergistic properties. Hence, such an inference is improper to be imported into an argument in support of a case of *prima facie* obviousness.

The presently claimed invention has been amended to clarify that the invention is directed toward a combination of amlodipine and hydroxylated atorvastatin, wherein said combination has synergistic properties. See, *e.g.*, FIG. 1, additionally, refer to Dr. Mason's Declaration (see, Exhibit B). Based on Dr. Jukema's Declaration, the cited reference used to construct a *prima facie* case of obviousness against the presently claimed invention, *i.e.*, his own paper, does not provide for any evidence of synergy between amlodipine and hydroxylated atorvastatin. Again, to impute any synergistic property based on Jukema would be improper and untenable.

Further, Dr. Jukema states in paragraph 7 of his declaration, "that our paper did *not* mention the use of atorvastatin as a combination agent or specifically suggest the use of amlodipine in combination with the HMG-CoA reductase inhibitor atorvastatin." [italics added] In fact, in paragraph 6 Jukema declares "that the REGRESS trial was *not* designed to evaluate combination therapy, specifically, a therapy combining a CCB with an HHMG-CoA reductase inhibitor." [italics added] These declarations clearly indicate that Jukema's paper cannot be used to supply the deficiencies present in Davison and Bjorge as correctly pointed out by the Examiner.

It must be appreciated that Jukema *et al.* is a retrospective analysis of a clinical investigation and it can be argued that it teaches away from our invention as it shows that patients on the combination of a CCB and statin actually had more adverse clinical events. Jukema *et al.* states that patients receiving the combination of a calcium channel blocker with the HMG-CoA reductase inhibitor pravastatin did *not* experience fewer adverse clinical events as compared to patients that were not on calcium channel blocker therapy with pravastatin. In fact, it was reported in the article that patients that were being simultaneously treated with both a calcium channel blocker and pravastatin actually had more cardiovascular complications (*e.g.*, more revascularization procedures) than patients not taking the treatment combination. Although the increase in adverse events with the drug combination was not statistically significant, it further argues against a synergistic therapeutic benefit based on this retrospective nonexperimental analysis. Jukema *et al.* recognized the combination of a calcium channel blocker with pravastatin improved anatomical changes in certain coronary vessels, as measured with angiographic approaches, but this did not correlate with an improvement in clinical outcomes - this is in contrast to Examiner's argument.

Dr. Jukema addresses this very point in his Declaration as well. In paragraph 14 he declares, "that the improved anatomical changes *i.e.*, angiographic changes in lumen size in certain coronary vessels following combination therapy did *not* correlate with a significant reduction in clinical events." [italics added] Further in paragraph 15 he declares, "that the reason for the anatomical changes may be due to confounding factors

and may not directly be related to the combination treatment." In paragraph 16 he declares, "that the absence of a correlation between significant changes in lumen size of the coronary artery (measured by angiography) clinical events may be due to the low number events in REGRESS but is also consistent with other angiographic-based trials at the time ..." Clearly, as evidenced by the authors own words, there is no correlation between improved anatomical features and combination therapy as claimed in the present invention.

The Examiner also cites the Merck Index stating that the Index "lists atorvastatin as a HMG-CoA Reductase Inhibitor, belonging to the same therapeutic group as Pravastatin ..." (Applicant assumes that the Examiner makes this statement due to the inclusion of pravastatin in the Jukema paper.) Dr. Jukema in his Declaration states "that I did not present data nor discuss that a synergistic effect observed with amlodipine and atorvastatin metabolite could be reproduced using other statins." Dr. Jukema by this declaration is informing us that one should not assume that it can be assumed that pravastatin will have the same effect as the atorvastatin metabolite when combined with amlodipine. Moreover, FIG. 5 illustrates this point where other statins were used in combination with amlodipine and a synergistic effect was not observed. Clearly, this suggests that there is a unique relationship between atorvastatin and amlodipine and that one cannot generalize at this time as to a combination of classes producing synergistic effects.

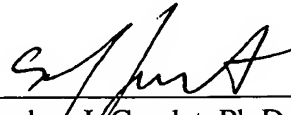
Clearly, as supported by the above discussion, there is nothing in Jukema that teaches or suggests the presently claimed invention. Moreover, Jukema lacks any motivation to one skilled in the art to combine either Davison, Bjorge and/or the Index with Jukema. Significantly, there is no reasonable expectation that if one were to combine these references that one would arrive at the presently claimed invention.

In conclusion, in view of the above amendments and remarks, Applicant respectfully requests the Examiner find the pending claims in condition of allowance and, therefore, issue a Notice of Allowance.

Although no fees are required, please charge any underpayment of fees to or credit any overpayment of fees to Deposit Account No. 03-2410.

The Examiner is invited to call the undersigned attorney at (617) 854-4237 should he determine that a telephonic interview would expedite prosecution of this case.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'S. J. Gaudet', written over a horizontal line.

Stephen J. Gaudet, Ph.D.
Attorney for Applicant
Reg. No. 48,921

Date: 4/28/04

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Mason, R.P.

Group Art Unit: 1617

Application Serial No.: 10/033,149

Examiner: Jiang, S.A.

Filed: October 19, 2001

For: Synergistic Effects of Amlodipine and Atorvastatin Metabolite as a Basis for
Combination Therapy

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

DECLARATION UNDER 37 CFR 1.132

I, J. Wouter Jukema, declare that I have the following qualifications in the field of
Medicine.

- I. Academic Rank and Advanced Degrees:
J.Wouter Jukema, MD, PhD, FESC, FACC
Associate Professor of Cardiology
Head Interventional Cardiology
Dept of Cardiology C5-P
Leiden University Medical Center

II. Current Position:

Currently I am a physician/researcher in the Department of Cardiology,
Leiden University Medical Center, the Netherlands.

I further declare:

- (1) that I am currently working as an active researcher in the area of vascular physiology/pharmacology;
- (2) that I have published peer reviewed articles in this area, one such paper is entitled "Evidence for a Synergistic Effect of Calcium Channel Blockers with Lipid-Lowering Therapy in Retarding Progression of Coronary Atherosclerosis in Symptomatic Patients with Normal to Moderately Raised Cholesterol Levels," published in *Arteriosclerosis, Thrombosis, and vascular Biology* (1996) 16:425-430; the following declarations are made in reference to this paper:
- (3) that the above-identified paper discusses a retrospective analysis of a clinical investigation, specifically, reviewing data obtained from the Regression Growth Evaluation Statin Study (REGRESS) trial;
- (4) that we did not conduct any original experiments for this analysis of the REGRESS study, such as data showing a synergistic effect using a combination therapy comprising amlodipine and atorvastatin (or any of their analogs);
- (5) that based on the fact that our study is a retrospective analysis, no definite conclusions can be drawn concerning the potential benefits of any therapeutic combination;

however, the analysis can be considered important for generating hypotheses requiring further investigation;

(6) that the REGRESS trial was not designed to evaluate combination therapy, specifically, a therapy combining a CCB with an HMG-CoA reductase inhibitor;

(7) that our paper did not mention the use of atorvastatin as a combination agent or specifically suggest the use of amlodipine in combination with the HMG-CoA reductase inhibitor atorvastatin;

(8) that three classes of CCBs were employed in the above-identified study, (i) 1,4-dihydropyridines (such as nifedipine, amlodipine, *et al.*), (ii) phenylalkylamine (such as verapamil), (iii) benzothiazepine (such as diltiazem);

(9) that the article indicated that “Whether all CCBs or only some of these drugs are capable of extending the antiatherosclerotic effect of pravastatin is not yet known”; further, that none of the calcium channel blockers listed in (8) above are indicated as being superior as a result of our retrospective analysis. The study did not show specific advantages for patients treated with a dihydropyridine calcium channel blocker as compared to representative non-dihydropyridine calcium channel blockers;

(10) that an antioxidant effect for the active metabolite of atorvastatin, independent of HMG-CoA reductase inhibition, was not appreciated at the time;

(11) that I did not present data nor discuss the notion that the antioxidant effect of the atorvastatin metabolite would be enhanced by amlodipine in a synergistic fashion;

(12) that I did not present data nor discuss that a synergistic effect observed with amlodipine and atorvastatin metabolite could be reproduced using other statins;

(13) that our analysis showed “no beneficial effects of CCBs on clinical events were observed” and specifically patients receiving a combination of a calcium channel blocker with an HMG-CoA reductase inhibitor did not experience fewer adverse clinical events as compared to patients that were not on such combination therapy;

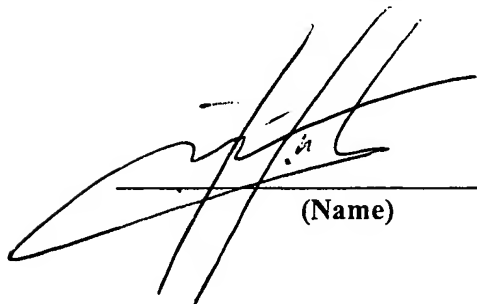
(14) that the improved anatomical changes *i.e.*, angiographic changes in lumen size in certain coronary vessels following combination therapy did not correlate with a significant reduction in clinical events. The scientific basis for this observation is not understood but may be due to the low incidence of events in REGRESS, confounding variables, or lack of therapeutic benefit.

(15) that the reason for the anatomical changes may be due to confounding factors and may not directly be related to the combination treatment;

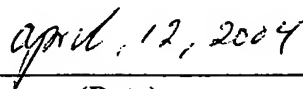
(16) that the absence of a correlation between significant changes in lumen size of the coronary artery (measured by angiography) clinical events may be due to the low number events in REGRESS but is also consistent with other angiographic-based trials at that time, as reviewed by Levine et al. *New England Journal of Medicine*, **332**:512-521 (1995).

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so

made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



(Name)



(Date)



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor application of: Mason, R.P.

Group Art Unit: 1617

Application Serial No.: 10/033,149

Examiner: Jiang, S.A.

Filed: October 19, 2001

For: Synergistic Effects of Amlodipine and Atorvastatin Metabolite as a Basis for Combination Therapy

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

DECLARATION UNDER 37 CFR 1.132

I, R. Preston Mason, Ph.D., declare that I have the following positions, education and qualifications in the field of biomedical science:

1. I am the President and Founder of Elucida Research in Beverly Massachusetts, an independent research laboratory dedicated to innovative biomedical research since 2000.
2. I am a faculty member in the Department of Medicine at Harvard Medical School in Boston, Massachusetts. I am also a senior research scientist at the Harvard – affiliated facility, Brigham and Women's Hospital in Boston.
3. I received my bachelor's degree in biology (*Summa Cum Laude*) from Gordon College in Wenham, MA in 1985. I received the Sarah Ball Award for the highest G.P.A. among all students majoring in science in 1984. Following graduation, I received a scholarship to attend the University of Connecticut School of Medicine (MD/PhD predoctoral fellowship) where I received a Ph.D. in 1985 in Biomedical Sciences with a concentration in Cell Biology and Biophysics. After graduation, I

received two consecutive post-doctoral fellowships from the American Heart Association, Connecticut Affiliate.

4. I joined the faculty at the University of Connecticut School of Medicine in 1991 as an assistant professor of radiology and an independent investigator in the Biomolecular Structure Analysis Center. In 1994, I moved to Pennsylvania as I was invited to join the faculty of MCP Hahnemann University School of Medicine (now part of Drexel University) as an associate professor of psychiatry, biochemistry and medicine until 2001 when I returned to New England.
5. My medical research interests broadly include membrane biophysics, oxidative stress, vascular biology and molecular pharmacology. A frequent lecturer at national and international meetings and academic seminars, I have written or coauthored more than 80 full-length articles and book chapters related to my research in journals such as *Circulation*, *Biochemistry*, *Journal of Biological Chemistry*, *Journal of Lipid Research* and *Journal of the American Medical Association*. This past year, I was invited to present my research in cardiovascular pharmacology at the annual meetings of the American Heart Association and the American College of Cardiology. I also co-chaired a scientific session at the American Heart Association annual meeting in 2003.
6. I have served as an expert scientific reviewer for the National Institutes of Health and the American Heart Association, Southeastern Pennsylvania Affiliate, for several years.

I further declare:

- (1) that I am currently working as an active researcher in the area of vascular physiology/pharmacology and study calcium channel blockers such as amlodipine and HMG-CoA reductase inhibitors, including atorvastatin and its active metabolite;
- (2) that I have supervised experiments in my laboratory in which I observed a strong *synergistic* antioxidant effect with amlodipine when combined with the active, o-hydroxy metabolite of atorvastatin, as shown in FIGURE 1A, specifically, the combination being an effective inhibitor of oxidation processes in human samples of low-density lipoprotein (LDL) in a manner that significantly exceeded their separate, additive effects, as shown in FIGURE 1B by more than two-fold;
- (3) that antioxidant activity for the combination of amlodipine and atorvastatin active metabolite is important since oxidized LDL contributes to the pathophysiology of atherosclerosis, including foam cell formation and endothelial dysfunction;¹

¹ As the underlying disease process in coronary artery disease, atherosclerosis is a leading cause of death in the United States and much of the developed world. The relationship between LDL oxidation and atherogenesis has been well characterized in the scientific literature (Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witztum JL. Beyond cholesterol. Modifications of low-density lipoprotein that increase its atherogenicity. *N. Engl. J. Med.* 1989;320:915-924; Steinberg D. Low density lipoprotein oxidation and its pathobiological significance. *J. Biol. Chem.* 1997;272:20963-20966)

(4) that the highly synergistic inhibition of LDL oxidation with the combination of amlodipine and atorvastatin metabolite could not be reproduced:

(a) by the combination of amlodipine with another HMG-CoA reductase inhibitor (lovastatin), as shown in FIGURE 2, and

(b) furthermore, the HMG-CoA reductase inhibitor lovastatin does not possess antioxidant activity, separately

these findings indicate that the synergistic effect was unexpected and may not be reproduced by the combination of amlodipine with other active HMG-CoA reductase inhibitors; and

(5) that the synergistic antioxidant effect of amlodipine and atorvastatin active metabolite was unexpected since it was observed with fixed levels of LDL under controlled, *in vitro* conditions.²

² As this experimental system did not contain contractile cells with calcium channels or hepatocytes with HMG-CoA reductase enzymes, the synergistic activity of the combination was independent of pharmacologic changes in either calcium flux or serum LDL levels.

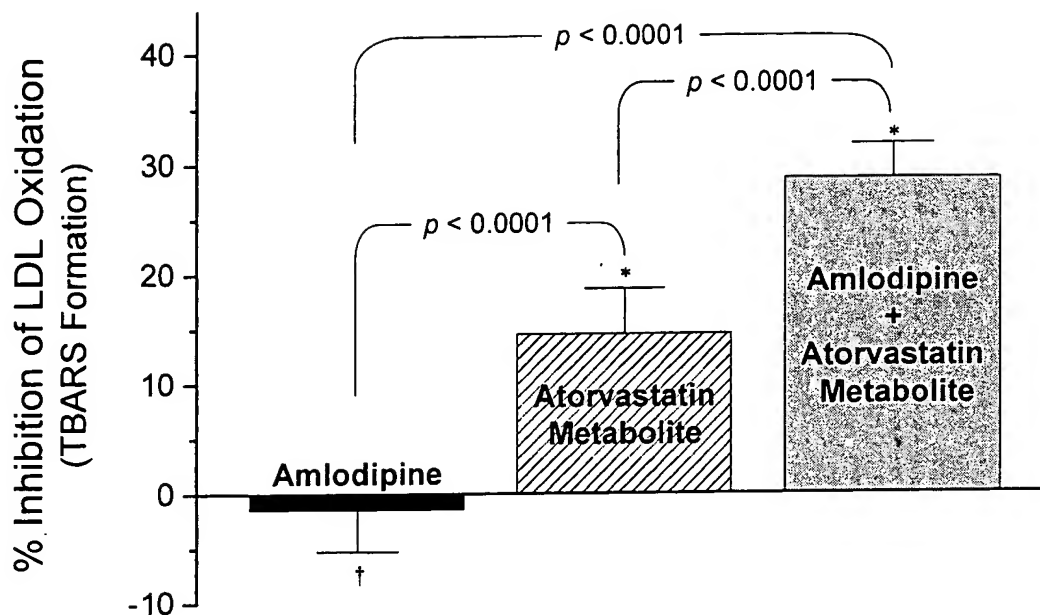
I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

RPW
(Name)

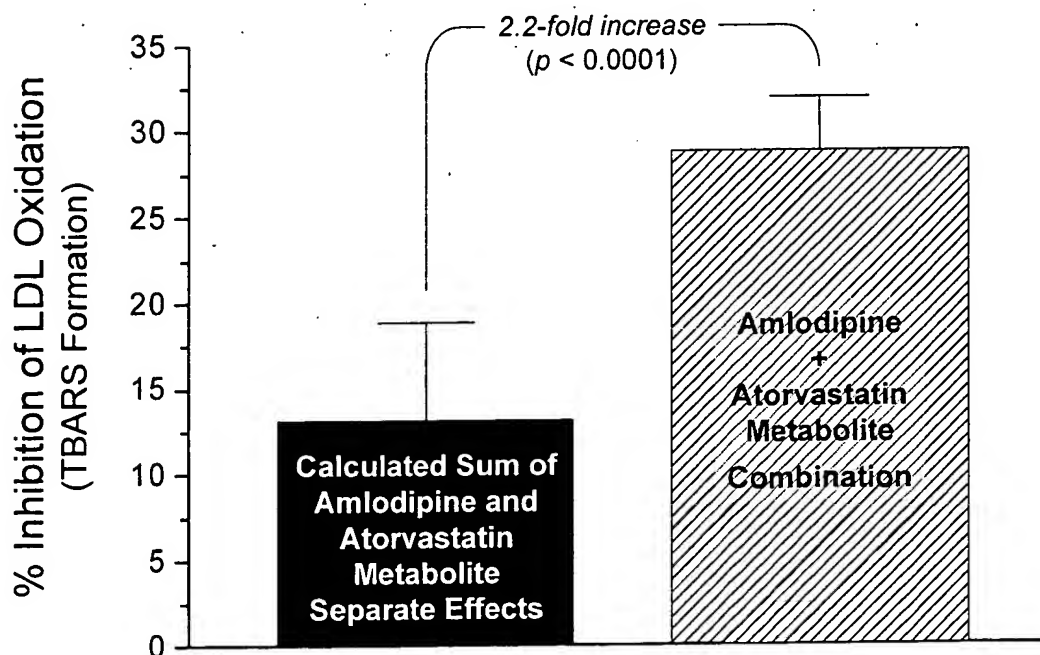
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Figure 1

A



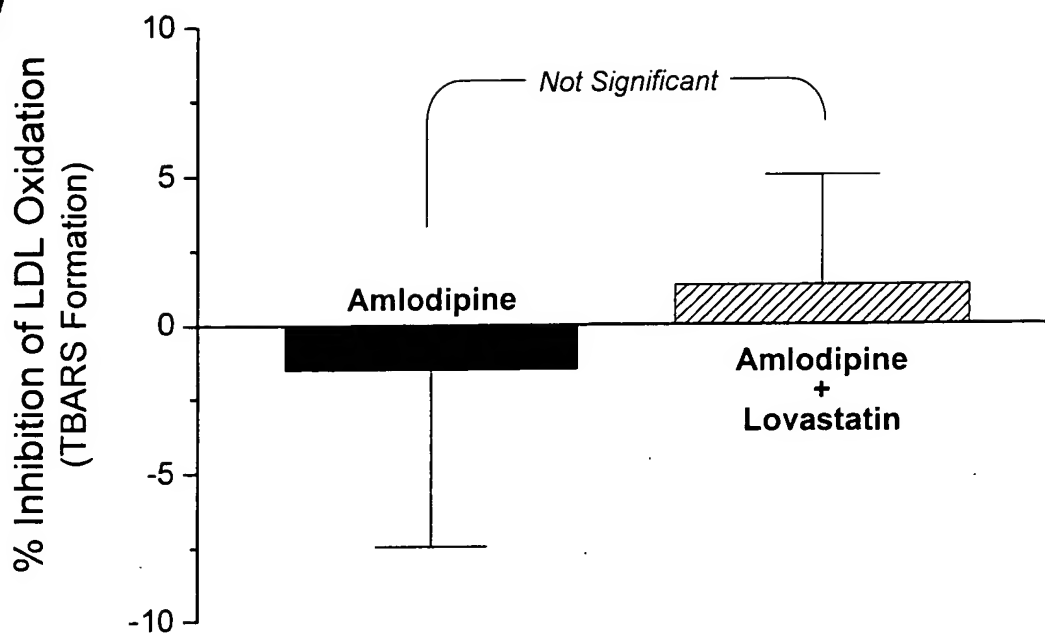
B



% Inhibition based on mean \pm SD

* $p \leq 0.0001$ versus control; † $p = 0.2754$ versus control

Figure 2



% Inhibition based on mean \pm SD